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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/813,781	03/07/97	WEIDANZ J	46745

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EXAMINER	
SCHWADRON, R	
ART UNIT	**PAPER NUMBER**
1644	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/813,781	Applicant(s) Weidanz et al.
	Examiner Ron Schwadron, Ph.D.	Group Art Unit 1644

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-4, 7-9, 13-15, 21-60, 62-64, 66-69, 71, and 72* is/are pending in the application.

Of the above, claim(s) *3, 9, 13, 15, 21-60, 62-64, 66, and 68* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 4, 7, 8, 14, 67, 69, 71, and 72* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The finality of the previous Office Action is withdrawn. The amendment filed 7/3/2000 has been entered. Claim 69 was amended. Claims 6,18-20,61,65,70,73,74 have been cancelled.

2. Claims 1, 2, 4, 7, 8, 14, 67, 69, 71, 72 are under examination as they read upon the elected species of TCR-bacteriophage coat protein fusion protein IE fusion protein comprising in sequence a V-α-peptide linker-Vβ-Cβ-bacteriophage coat VIII protein.

3. Claims 1, 2, 4, 7, 8, 14, 67, 69, 71, 72 are rejected under 35 U.S.C. 103(a) as unpatentable over WO 96/18105 (issued 13 June 1996) in view of Barbas US 5,759,817 (filed Jan. 27, 1992), Onda et al. (Molecular Immunology 32:1387, 1995), and Huse et al. J. Immunology 149:3914, 1992

WO 96/18105 teaches a single chain T cell receptor which specifically binds to peptide ligand (see abstract). WO 96/18105 further teaches one embodiment of human single chain TCR in which C-terminus of V α domain is linked to N-terminus of V β chain via a 15 amino acid residue flexible amino acid liner and the C-terminus of the V β chain is linked to the beta chain constant domain (see pages 3 and 5 and Figure 1, in particular). In one embodiment the C terminus of V β chain is linked to a alkaline phosphatase (PI) protein tag (see Figure 1, in particular). WO 96/18105 also teaches that the order of the domains within the single chain TCR is interchangeable (see page 5, in particular). WO 96/18105 also teach that the purpose of the linker is to enhance the binding characteristics of the soluble T cell receptor and that linkers of about 10 to 30 amino acid residues would be considered to be sufficient. WO 96/18105 also teach that a preferred embodiments of linkers are composed of amino acids which tend to increase solubility in aqueous solution (see page 8, lines 1-25, in particular). WO 96/18105 further teach that the TCR fusion protein comprising V-α-peptide linker-V β-C β fusion protein can be linked to additional segments which do not interfere with the essential properties of the encoded molecule (see page 8, lines 5-8, and page 9, lines 1-9, in particular). WO 96/18105 disclose that the TCR fusion protein can bind antigenic protein, thus teaching that the TCR fusion protein comprises an antigen binding pocket. WP 96/18105 exemplifies a TCR fusion protein comprising V-α-peptide linker-V β-C β linked to GPI anchor and expression of

such a fusion protein in a transfected eukaryotic cell (see page 17, lines 13-31, in particular). WO 96/18105 further disclose that the soluble form of TCR protein could be readily obtained by enzymatic cleavage with phosphatidylinostol-specific phospholipase C (PI-PLC) (see page 17, lines 23-24, in particular). WO 96/18105 also teaches expression of said TCR fusion protein in a bacterial cell system in which the N terminus of the Cβ region is linked to a histidine protein tag (see pages 26-30, in particular). Additionally WO 96/18105 also disclose a scTCR in which comprises V-α-peptide linker-V β-C β GPI in which the Cβ component consists of the β chain sequence ending right before the last cysteine (the sixth cysteine) (see page 21, lines 20-32, in particular). WO 96/18105 further teach that TCR fusion proteins which do not contain the CB do not fold into the native conformation (see page 30, line through page 31, line 31, in particular). The scTCR disclosed by WO 96/18105 meet the length limitations of the Vα and Vβ region recited in claims 69 and 71 since the term "about 200 to about 400" and "about 50-126" has been interpreted broadly to encompass the length of Vα and Vβ. components of the scTCR taught by WO96/18105. The W0 96/18105 further teaches that the single chain TCR may be derivatized by conjugation of group which does not alter the binding characteristics of the single chain TCR (see page 9, lines 2-20, in particular). Thus WO 96/18105 teach a soluble fusion protein comprising a Vα-peptide linker-Vβ-Cβ fragment-protein tag. WO 96/18105 does not teach a TCR fusion protein further comprising bacteriophage VIII coat protein. However, Barbas discloses a soluble fusion protein comprising a bacteriophage coat protein fragment covalently linked to a single-chain heterodimeric receptor (see abstract and column 15, lines 27-28, in particular). Barbas also discloses that the fusion protein may comprise domains of heterodimeric proteins derived from several ligand binding proteins, including immunoglobulins and T cell receptors (see column 17, lines 62-66 and column 19, lines, 9-28. Barbas discloses that T cell receptor comprises alpha and beta chains each having a variable(V) and constant(C) region and T cell receptor has similarities in genetic organization and function to immunoglobulins (see column 19, lines 19-22, in particular). Barbas also teaches that bacteriophage coat protein may be derived from cpIII or cpVIII (see column 31, lines 10-28, in particular). Barbas discloses that expression vectors expressing soluble fusion proteins in which the ligand binding region is fused to bacteria coat protein allows the

expression of the multiple fusion proteins on the surface of phage particles IE approximately 2700 cpVIII heterodimer receptor molecules per phage particle (see column 39 line 64 through column 40, line 7, in particular). Barbas further discloses that a short length of amino acid sequence at the amino end of a protein (IE a protein tag) directs the protein to periplasmic space (see column 8, lines 49-55, in particular. One embodiment of the invention is disclosed to be a fusion protein comprising in sequence a leader sequence-peptide linker-V region amino acid residue-peptide linker -phage coat protein and that in one embodiment, the second linker can define a proteolytic cleavage site which allows the heterodimeric receptor to be cleaved from the bacteriophage coat protein to which it is attached (see column 14, lines 60-65). Thus Barbas discloses but does not exemplify a soluble fusion protein comprising a bacteriophage coat protein covalently linked to T cell receptor domains. Onda et al_.disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain T cell receptor by a peptide linker sequence wherein the single TCR chain is the alpha chain and the bacteriophage coat protein is cpVIII (see abstract and Figure 1, in particular). Onda et al. also teach that TCR-bacteriophage coat protein fusion protein can be used to study specific binding interactions of the TCR chain to antigenic ligands (see paragraph bridging pages 1394-1395, in particular). Huse_et al. teach that fusion proteins comprising a single chain fusion protein comprising Fab fragment of immunoglobulin (which comprises the antigen binding pocket of the immunoglobulin molecule) and bacteriophage VIII coat protein can be produced and display the fusion protein when expressed in a M13 derived vector. Huse et al. further teach that bacteriophage VIII coat protein fusion protein can recovered from culture medium or from the periplasmic space (see abstract).

Therefore it would have been prima facie obvious to one with ordinary skill in the art at the time the invention was made to make a soluble TCR fusion protein comprising the Vα.-peptide linker-Vβ-Cβ fragment component taught by WO 96/18105 linked to a bacteriophage VIII coat protein because Barbas et al. and Onda et al. teach TCR-bacteriophage VIII coat fusion proteins can be used to study antigen binding properties of such a fusion protein and Huse et al. teach that fusion proteins comprising bacteriophage VIII coat protein can be produced in bacteria and recovered in relatively large quantities. One with skill in the art would be motivated to make such a fusion protein to study the antigen binding region of the TCR component or to use the protein to elicit anti-idiotypic

antibodies. One with skill in the art would be motivated to make such a fusion protein in which the Vα and Vβ region was derived from human TCR in order to study human TCR properties or to elicit anti-idiotypic antibodies to the TCR component of the protein.

Regarding the 131 declaration filed Dec. 27, 1999, said declaration does not address the claimed invention (eg. the protein of claim 1 which contains a Cβ **fragment**).

4. Claims 1, 2, 4, 7, 8, 14, 67, 69, 71, 72 are rejected under 35 U.S.C. 103(a) as unpatentable over Chung et al. in view of Barbas US 5,759,817 (filed Jan. 27, 1992), Onda et al. (Molecular Immunology 32:1387, 1995), and Huse et al. J. Immunology 149:3914, 1992

Chung et al. teaches a single chain T cell receptor which specifically binds to peptide ligand (see abstract). Chung et al. further teaches one embodiment of human single chain TCR in which C-terminus of V α domain is linked to N-terminus of V β chain via a 15 amino acid residue flexible amino acid liner and the C-terminus of the V β chain is linked to the beta chain constant domain (see Figure 1). In one embodiment the C terminus of V β chain is linked to a alkaline phosphatase (PI) protein tag (see page 12655). Chung et also teach that the purpose of the linker is to enhance the binding characteristics of the soluble T cell receptor and that linkers of about 10 to 30 amino acid residues would be considered to be sufficient. Chung et al. teach that the TCR fusion protein can bind antigenic protein, thus teaching that the TCR fusion protein comprises an antigen binding pocket. Chung et al. teaches a TCR fusion protein comprising V-α-peptide linker-V β-C β linked to GPI anchor and expression of such a fusion protein in a transfected eukaryotic cell (see results section). Chung et al. disclose that the soluble form of TCR protein could be readily obtained by enzymatic cleavage with phosphatidylinostol-specific phospholipase C (PI-PLC) (see page 12656). Chung et al. teaches expression of said TCR fusion protein in a bacterial cell system in which the N terminus of the Cβ region is linked to a histidine protein tag. Chung et al. also disclose a scTCR in which comprises V-α-peptide linker-V β-C β GPI in which the Cβ component consists of the β chain sequence ending right before the last cysteine (the sixth cysteine) (see page 12655). Chung et al. further teach that TCR fusion proteins which do not

contain the CB do not fold into the native conformation. The scTCR disclosed by Chung et al. meet the length limitations of the Vα. and Vβ region recited in claims 69 and 71. Chung et al. teach a soluble fusion protein comprising a Vα-peptide linker-Vβ-Cβ fragment-protein tag (eg. GPI). Chung et al. does not teach a TCR fusion protein further comprising bacteriophage VIII coat protein. However, Barbas discloses a soluble fusion protein comprising a bacteriophage coat protein fragment covalently linked to a single-chain heterodimeric receptor (see abstract and column 15, lines 27-28, in particular). Barbas also discloses that the fusion protein may comprise domains of heterodimeric proteins derived from several ligand binding proteins, including immunoglobulins and T cell receptors (see column 17, lines 62-66 and column 19, lines, 9-28. Barbas discloses that T cell receptor comprises alpha and beta chains each having a variable(V) and constant(C) region and T cell receptor has similarities in genetic organization and function to immunoglobulins (see column 19, lines 19-22, in particular). Barbas also teaches that bacteriophage coat protein may be derived from cpIII or cpVIII (see column 31, lines 10-28, in particular). Barbas discloses that expression vectors expressing soluble fusion proteins in which the ligand binding region is fused to bacteria coat protein allows the expression of the multiple fusion proteins on the surface of phage particles IE approximately 2700 cpVIII heterodimer receptor molecules per phage particle (see column 39 line 64 through column 40, line 7, in particular). Barbas further discloses that a short length of amino acid sequence at the amino end of a protein (IE a protein tag) directs the protein to periplasmic space (see column 8, lines 49-55, in particular. One embodiment of the invention is disclosed to be a fusion protein comprising in sequence a leader sequence-peptide linker-V region amino acid residue-peptide linker -phage coat protein and that in one embodiment, the second linker can define a proteolytic cleavage site which allows the heterodimeric receptor to be cleaved from the bacteriophage coat protein to which it is attached (see column 14, lines 60-65). Thus Barbas discloses but does not exemplify a soluble fusion protein comprising a bacteriophage coat protein covalently linked to T cell receptor domains. Onda et al .disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a single-chain T cell receptor by a peptide linker sequence wherein the single TCR chain is the alpha chain and the bacteriophage coat protein is cpVIII (see abstract and Figure 1, in particular). Onda et

al. also teach that TCR-bacteriophage coat protein fusion protein can be used to study specific binding interactions of the TCR chain to antigenic ligands (see paragraph bridging pages 1394-1395, in particular). Huse et al. teach that fusion proteins comprising a single chain fusion protein comprising Fab fragment of immunoglobulin (which comprises the antigen binding pocket of the immunoglobulin molecule) and bacteriophage VIII coat protein can be produced and display the fusion protein when expressed in a M13 derived vector. Huse et al. further teach that bacteriophage VIII coat protein fusion protein can recovered from culture medium or from the periplasmic space (see abstract).

Therefore it would have been prima facie obvious to one with ordinary skill in the art at the time the invention was made to make a soluble TCR fusion protein comprising the Vα.-peptide linker-Vβ -Cb fragment-protein taught by Chung et al. linked to a bacteriophage VIII coat protein because Barbas et al. and Onda et al. teach TCR-bacteriophage VIII coat fusion proteins can be used to study antigen binding properties of such a fusion protein and Huse et al. teach that fusion proteins comprising bacteriophage VIII coat protein can be produced in bacteria and recovered in relatively large quantities. One with skill in the art would be motivated to make such a fusion protein to study the antigen binding region of the TCR component or to use the protein to elicit anti-idiotypic antibodies. One with skill in the art would be motivated to make such a fusion protein in which the Vα and Vβ region was derived from human TCR in order to study human TCR properties or to elicit anti-idiotypic antibodies to the TCR component of the protein.

5. No claim is allowed.

6. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 1600 at (703) 308-4242.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Monday through Thursday from 7:30 to

6:00. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Ron Schwadron, Ph.D.
Primary Examiner
Art Unit 1644

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1600